Ninth Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction

13 December 2022

English only

Geneva, 28 November – 16 December 2022
Item 10 of the provisional agenda
Review of the operation of the Convention as provided for in its Article XII

New scientific and technological developments relevant to the Convention

Background information document submitted by the Implementation Support Unit

Summary

The Preparatory Committee decided to request the Implementation Support Unit (ISU) to prepare a background information document on new scientific and technological developments relevant to the Convention, to be compiled from information submitted by States Parties as well as from information provided by relevant international organisations (see BWC/CONF.IX/PC/10, paragraph 36). The ISU duly requested submissions from States Parties, and all submissions provided to the ISU by 30 November 2022 are included in this document. Any further submissions from States Parties will be included in an addendum to this document. The information in this document is reproduced as submitted by States Parties, in some cases with minor editing. Information submitted in official languages other than English has been translated into English.

Contents

Cuba

1. Cuba has always supported a well-organized and systematic review of new scientific and technological developments and an evaluation of the application of those developments in respect of the Biological Weapons Convention and the States parties to the Convention.

2. The implementation of the Convention cannot depend on a review of new developments in science and technology. Nor can it be used as a pretext to limit the exchange or use of biological agents and toxins for peaceful purposes. Dual uses are not in themselves a reason to hinder prohibit or restrict the fullest possible exchange of information on new developments in science and technology.

3. This is a cross-cutting issue. Science and technology are the basis of several articles of the Convention and have also been addressed in specific contexts – for example, the Ad Hoc Meeting of Scientific and Technical Experts of States Parties to Finalize Modalities for the Exchange of Information and Data, which was held in 1987 to develop forms for confidence-building measures, and the Ad Hoc Group of Governmental Experts to Identify and Examine Potential Verification Measures from a Scientific and Technical Standpoint (VEREX), which met from 1992 to 1993.

4. Cuba has participated in all the processes mentioned above, as well as in the Ad Hoc Technical Expert Group on Synthetic Biology within the framework of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, and the country's main national positions and experiences are reflected in documents BWC/MSP/2018/MX.2/WP.10, BWC/MSP/2018/MX.2/WP.11 and BWC/MSP/2020/MX.2/WP.12, as well as in several statements, including those made in the most recent intersessional period.

5. The scope of the review of scientific and technological developments relevant to the Convention is very broad. In this context, tools such as gene editing, especially those related to CRISPR/Cas techniques, as well as those related to ongoing progress in synthetic biology, have been addressed.

6. To address concerns about accidental releases into the environment and in ecosystems, as well as other incidents, the potential for organisms and products resulting from synthetic biology to cause harm should be subjected to a risk assessment from the outset of the research design.

7. The aim is for these assessments to be a prerequisite for approval by national authorities, regardless of the peaceful use that is planned. A system with a national coordination mechanism, a legal framework, standards and guidelines, national codes of conduct, self-governance and an additional national supervisory authority could enhance transparency, encourage the development of a culture of safety and promote responsible behaviour, thereby addressing these concerns. The aim is not to institute prohibitions but to ensure the adoption of responsible and effective regulation that maintains the rights of all States parties to develop this emerging technology in a safe environment, in accordance with articles X and III of the Biological Weapons Convention.

8. Cuba has a national biosafety and biosecurity system. Its fundamental objectives include guaranteeing the health of workers, implementing the provisions of the Convention and other international instruments (the Convention on Biological Diversity and the protocols related to biosafety), preserving the environment and, to prevent possible bioterrorism, guaranteeing safe conditions in respect of biological agents, the provision of information and the relevant facilities.

9. For that purpose, a specific legal framework for biosafety and biosecurity, which involves 13 legal instruments and 4 technical norms, as well as a monitoring mechanism (inspections and authorizations) to ensure safe conditions, was developed from 1996 to 2020 (much of it updated in the period 2018–2020). Worthy of note in this respect are:

- Official Gazette, Ordinary No. 93, 1 September 2022, Act No. 151/2022, Criminal Code (GOC-2022–861-O93)

- Official Gazette, Ordinary No. 52, 23 July 2020, Decree-Law No. 4/2020 on the National Commission for the Use of Genetically Modified Organisms in Cuban Agriculture (GOC-2020–502-O52)
- Official Gazette, Ordinary No. 65, 18 September 2020, Decree-Law No.10/2020 on the National Regulatory Authorities (GOC-2020–602-O65)
- Decree No. 17/2020, Implementing Regulations of the Decree-Law on the National Regulatory Authorities (GOC-2020–603-O65)
- Resolution No. 199/2020, Biosafety regulations for the use of biological agents and their products, organisms and fragments with genetic information (GOC-2020–505-O52)

Switzerland

10. In line with the requested background information for the Ninth Review Conference of the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, in particular the request for background information on new scientific and technological developments relevant to the Convention as contained in document BWC/CONF.IX/PC/2, Switzerland submits the following report to States Parties.

I. Introduction

11. Developments in science and technology lay the foundation to increase well-being, health and consequently prosperity worldwide. Switzerland places great emphasis on supporting and creating the best environment for researchers and developers to advance their ideas and inspire innovation. However, Switzerland is also convinced of the need to carefully monitor these developments, in particular regarding their dual-use potential. To monitor advances in science and technology with potential relevance to the Biological and Toxins Weapons Convention and the Chemical Weapons Convention, Switzerland established the conference series Spiez CONVERGENCE. The results of our monitoring efforts regarding advances in chemistry, biology and associated fields as well as the reasoning behind it, are well documented. In the following, we highlight some developments that are of particular significance.

II. DNA-synthesis and synthetic biology

12. Synthesis of short sequences of DNA (10-20 basepairs (bp)) can be used in PCR for the detection of longer stretches of nucleic acids e.g. from viruses or bacteria and thus, these are instrumental in disease surveillance. Longer sequences (≈ 1000 bp) that can encode genes for proteins and even longer sequences would enable researchers to synthesize complete plasmids or even small genomes. However, due to technical issues, current synthesis efforts barely extend beyond 3 kb. The methodology of DNA-synthesis has been around for years; however, it still struggles from low sequence accuracy for longer stretches. Recent methodological advances are expected to leap forward the efficiency and accelerate the field of synthetic genomics (see BWC/MSP/2019/MX.2/WP.2 for an earlier technology assessment).

13. Conventional error correction is laborious. Enzymatic error correction (EEC) can reduce errors in small DNA strands but would require prohibitive numbers of colonies for long DNA sequences. One way of addressing the issue of error removal is binary assembly error removal. This involves three core technologies, each of which is still under development: a thermal control chip made up of thousands of pixels that can each be controlled independently; advances in phosphoramidite chemistry to allow thermally controlled synthesis of single-stranded DNA on a chip; and on-chip assembly of single DNA strands into double-stranded DNA with error removal during assembly.

14. On the thermal control chip, each of the thousands of thermal pixels controls the temperature in the liquid above, thus creating "virtual wells" within a continuously flowing liquid. These islands of heat are used for the synthesis of short DNA oligomers. Because each pixel has independent and precise thermal control, the chip enables the parallel directing of synthesis of many single-stranded DNA molecules. These DNA molecules are then selectively released from the surface and flushed to another pixel for on-chip assembly into double-stranded DNA. Synthesis errors are detected and removed through thermal purification during the assembly into double-stranded DNA: heteroduplex DNA melts at a slightly lower temperature than a strand that has an accurate match, thus raising the temperature to just below melting point of the homoduplex will thermally remove mismatching DNA sequences.

15. This technology is at the prototype stage: the ability to create virtual wells in a flowing liquid has been demonstrated for a limited number of pixels, the thermally controlled synthesis approach has been shown to accurately synthesize single stranded DNA with all four bases, and a crucial step in the error-removal assembly has been demonstrated.

16. Future plans include the use of a modular platform that utilises single-use application-specific cartridges for parallel DNA synthesis, a plug-and-play benchtop instrument, and user interfaces, design algorithms and portals implemented in the cloud. Instruments planned further down the line are to address demands for rapid iteration of gene designs and prototyping, shorter synthesis turn-around times, greater lengths and complexities of the DNA, highly parallel synthesis and access to high-fidelity DNA. This will provide researchers with modular third-generation bench-top DNA synthesis capability for rapid synthesis with high accuracy, implementing different functionalities. This can be interfaced with cloud-based synthesis services and machine learning tools to accurately predict key parameters.

17. The (mis)use potential associated with synthetic cells or synthesis of long, highly accurate bench-top synthesis of DNA, goes far beyond that of today's genome cloning. Algorithms are becoming better in changing naturally occurring sequences to make them amicable for *in silico* platforms, and access to these technologies is getting easier. Commercial access to large DNA constructs is going to lower the level of human expertise required as well as the need for wet-lab infrastructure. The consequences of the growing access to tools of synthetic biology has yet to be fully understood.

III. Genetic Engineering

18. Nucleic acid synthesis lays the foundation for many more technologies and is the basis for synthetic biology. It was also instrumental for the discovery and characterization of CRISPR, which is now in use for the effective and targeted introduction of modifications. CRISPR has seen a sharp rise in applications, involved companies and license applications for *in vivo* use. However, concerns about its risks when used maliciously or its unintended consequences when used in combination with a gene drive have also increased.

19. Methods for site-directed introduction of mutations in easy-to-study model organisms or cell culture have been investigated for some years. Zink-Finger Nucleases allow the introduction of sequence-specific breaks in DNA. One domain of the nuclease had to be carefully designed to navigate the nuclease to its site of action while the other domain then cuts the DNA. Due to insufficient understanding of protein structure and its affinity and specificity to DNA stretches, the large-scale applicability of the technology was hampered. Similarly, Transcription activator-like effector nucleases (TALENs) were successfully applied to modify several genomes, however, they also require significant optimisation to be sufficiently specific.

20. The discovery of CRISPR and its subsequent development for different applications paved the way for large scale modification of organisms to characterize each and every of their genes and consequently greatly contributed to our understandings of basic biology. Furthermore, the targeted and specific introduction of mutations can make crops more resistant to climate change, or plant diseases, or alter their nutrient composition and increase yields.

21. The European Union considered CRISPR similar to other techniques that generate genetically engineered organisms (GMO) but recent reports suggest to re-think this ruling.

22. Currently, ten CRISPR-based applications are in a pre-commercial stage, of which seven are modified plants. From a legal and regulatory point of view, modification of plants is easier and the tested modifications include changes to the nutrient composition, stress or herbicide tolerance but possibilities range further. The advances in CRISPR might allow for the generation of plants that are immune against some pathogens, including those that were suspected in biological weapons programs.

23. The use of CRISPR in gene drives sparked much enthusiasm, especially in the field of vector control. Gene drives are genetic elements that encode the CRISPR-Cas system and if correctly designed, allow the spread of the gene drive within a given population. A gene drive could for example make mosquitoes infertile and thus extinct a species potentially together with the diseases it carries. However, due to concerns regarding the impact of the eradication of some vectors and the irreversibility thereof, their field application is currently on hold. Similarly, gene drives could also extinct useful species and CRISPR-based genome modification could make them more susceptible to pathogens, climate change or herbicides, which would pose a great risk to food security, health security but also biosecurity. More recently, different possibilities to stop the effects of CRISPR, more specifically Cas9, have gained attention. These inhibitors would render the application of CRISPR safer and equip us with tools against uncontrolled spread of gene drives.

IV. Analytic Technologies

24. Novel combinations of measurement technologies, higher sensitivities of these devices and increasingly sophisticated algorithms to analyse the vast amount of data generated will also equip the scientific community with tools to investigate modification signatures or purification artifacts. From a laboratory perspective, these advances might increasingly support efforts aimed at the attribution of a suspected breach of the Convention.

V. Preparedness and Response: mRNA-Vaccines

25. Preparedness is expensive. One way to protect humans and animals against infectious diseases is vaccination. However, most existing vaccines need different production and purification platforms increasing both development time and investments. Additionally, the requirements in terms of their quality control procedures are different. If countries want to invest in pandemic preparedness and have production facilities ready to produce vaccines, these facilities should preferably be usable for several different applications. mRNA-vaccines and the use of the same platform for production, formulation and quality control for vaccines against different diseases makes it possible to produce batches of different vaccines with the same equipment and thus decrease the overall cost of the vaccines but also the costs of pandemic preparedness.

26. Furthermore, the development of such vaccines and their licensing has and will continue to become faster, as companies and licensing officials adapt and streamline their methods.

VI. Conclusions

27. Many scientific and technological developments have the potential to simplify or refine the development of biological weapons with novel methodology or more advanced techniques, which poses challenges to the Convention. At the same time, however, many advances support the implementation of, and ensuring respect for, the Convention in areas such as protection, detection, preparedness and response. Monitoring and reviewing such advances is of crucial importance to assess the impact of developments in science and technology in terms of both their risks and benefits, and ultimately enable as well as facilitate facts-based decision-making in the framework of the Convention and beyond.

28. Switzerland will continue its efforts in monitoring science and technology developments, including by offering Spiez CONVERGENCE as an established platform for in-depth exchanges between scientists, practitioners, industry representatives, arms control experts and policymakers.

United Kingdom of Great Britain and Northern Ireland

29. This paper summarises some key points emerging from the 2017-2020 Standing Agenda Item on review of developments in the field of science and technology (S&T) related to the BTWC. It highlights some common understandings reached on the specific topics covered, as well as some areas that States Parties identified as requiring further consideration. These could provide some options for topics to be addressed in future reviews of science and technology, which are mentioned in the concluding paragraph.

I. Introduction

30. During the 2017-2020 Intersessional Programme (ISP), under the Standing Agenda Item on the review of developments in the field of science and technology related to the Convention, States Parties had the opportunity to reach common understandings and identify effective action on a wide range of relevant scientific topics. The review process included not only the provision of information on progress in various fields, but also consideration of the implications of developments on potential risks and benefits for the Convention, and on other possible measures such as:

- Biological risk assessment and management;
- Voluntary codes of conduct and other measures to encourage responsible conduct by scientists, academia, industry and civil society;
- And education and awareness raising about the risks and benefits of life sciences and biotechnology.

31. Many areas relating to S&T also have relevance to Article VII and Article X of the Convention. As such, reference will be made when cross cutting themes are also relevant to Articles VII and X, as they are intimately linked to S&T.

II. Genome editing

32. During the 2017-2020 ISP one particular scientific field became the ‘hot topic’ of discussion among BTWC States Parties, and indeed the world. Genome Editing dominated discussions and working papers throughout this ISP. Genome editing is a term encompassing many different molecular techniques for making changes to the genetic sequence of a given organism. These can range from restriction enzyme based techniques such as Transcription activator-like effector nucleases (TALENs), endonuclease techniques such as zinc-finger nuclease (ZFN), and the most widespread approach, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). CRISPR technology exploits the functionality of Cas (CRISPR-associated) proteins such as Cas9. The rapid rise in CRISPR-Cas9 technology has led to an explosion of research in this area. The potential applications, both for eukaryotic gene editing and prokaryotic ‘recombineering’, means that more and more groups are investing in CRISPR-Cas9. However, with the dawn of this new technology, there are rising concerns about the ethics of gene editing, how to regulate it now and its future use in gene therapy, agriculture and gene drives. CRISPR-Cas has the potential to enable editing of any gene, by deletion, insertion or control of expression, in virtually any organism. This has produced many start-up companies aiming to use CRISPR-Cas as a gene therapy for acquired or inherited diseases from HIV and cancer to muscular dystrophy and sickle cell anaemia. However, concerns over the use of CRISPR-Cas to make heritable changes to the human genome and lack of regulation surrounding “gene drives”, also highlight a potential for misapplication or deliberate misuse. Easy access to CRISPR-Cas9 reagents and the simplicity

of the technology portends towards ever more widespread use, with CRISPR-Cas9 quickly becoming a standard molecular microbiology tool in laboratories around the world.

33. A key advantage of using CRISPR-Cas9 is its simplicity, allowing it to be utilised in any molecular biology laboratory without the need for additional specialist equipment. There are a huge number of CRISPR-Cas9 tools are widely available online and are accessible to all, including non-professional scientists and so-called 'biohackers'. The inventors of the technology have made all of their tools open access, including full step-by-step guides to planning and executing CRISPR experiments. However, despite the easy access to online protocols, some tacit knowledge and experience of molecular biology techniques, and access to reagents such as restriction enzymes and competent cells, is still required.

34. Genome editing has the potential to provide benefits across an increasing number of areas, including in human health, agriculture and the environment. There could also be benefits of relevance to implementation of the BTWC, for example, providing support or assistance in response to a violation of the Convention under Article VII, and development and application of scientific discoveries to the prevention of infectious disease under Article X.

35. CRISPR technology has been developed to prevent and treat disease in humans, to modify plants to deal with the impacts of climate change and plant pathogens, and to halt the spread of viruses in animal populations. It can also be used to edit germline cells in embryos, introducing genetic changes that will be passed on to future generations and which could have potential in the treatment of genetic disorders. Some specific examples of beneficial genome editing applications given in a Royal Society Conference Report include[1]:

- Conferring resistance to porcine reproductive and respiratory disease virus in pigs and to the infectious pancreatic necrosis virus in Atlantic salmon;
- Targeted mutagenesis to prevent rice blast disease;
- Creation of improved cellular and animal models of disease to understand disease pathways, identify and validate novel drug targets and test the efficacy of new medicines;
- Targeting the genes involved in the symbiosis signalling pathway in barley to help understand their function. This may allow engineering of the pathway for cereal recognition of nitrogen-fixing bacteria, and support the development of nitrogen-fixing cereals, which could play an important role in global food sustainability.

36. The broader debate on the socio-economic implications of genome editing has tended to focus on the key ethical, moral and public perception aspects, though there has been some consideration of potential security concerns. In October 2017, the InterAcademy Partnership (IAP) convened an international workshop to assess the security implications of genome editing technology. Its major goal was to enable members of the research, security and policy communities, with wide geographical representation, to discuss potential benefits, security implications associated with intended misuse, and what might be done to prevent or mitigate potential harm[2]. Discussions focussed on specific applications of genome editing, including: human cell editing; agriculture (plants and animals); gene drive applications; and microbial applications. Participants identified beneficial applications similar to those mentioned in the Royal Society report; additional examples included:

- Developing gene drives to control insect vectors of diseases such as malaria;
- Transgenic cattle for increased resistance to tuberculosis;
- Development of screens for biological processes or disease;

[1] https://royalsociety.org/-/media/events/2018/03/crispr-revolution-tof/TOF-crispr-revolution-report.pdf?la=en-GB&hash=6BEBEE3995AFE423F97A5F213E91882E

[2] Fears R and ter Meulen V (2018) Assessing Security Implications of Genome Editing: Emerging Points From an International Workshop. Front. Bioeng. Biotechnol. 6:34. doi: 10.3389/fbioe.2018.00034

- Increased understanding of CRISPR functionality in bacteria revealing new opportunities to tackle pathogens, including the major therapeutic goal to avoid development of antimicrobial resistance.

37. At the workshop, potential security concerns, specifically intentional misuse, were explored taking account of developments in the specific applications. Issues included:

- Human cell editing concerns such as: influencing future human generations; misuse potential for 'off-label' use, for example using a medical product for a muscle disorder for enhancement of military capabilities; risk of genome editing viral vectors reaching unintended recipients;
- Microbial applications have the potential for misuse to construct or alter pathogens suitable for weaponisation - this would be of concern in both human health and agriculture;
- Gene drive applications could potentially be misused to create threats to human health (e.g., by increasing the transmission of infectious disease by insect vectors) and agriculture (e.g., by increasing insect pests and plant damage).

38. In assessing both potential benefits and risks, it is also important to consider the present and future limitations of the technology and what barriers would have to be overcome to address the challenges. Some examples of limitations include:

- Unwanted off target effects which can confound research experiments and present problems for therapeutic applications; development of more specific variants of CRISPR system enzymes could minimise these effects;
- Pre-existing immune responses in humans to proteins in the CRISPR-based technology; this may hinder use to treat disease and could cause significant toxicity to patients; utilisation of alternative enzyme variants may address this;
- Delivery to the target population based on viral-vector systems, which have limitations on size of insert, efficacy and specificity; new approaches being explored include utilisation of gold nanoparticles complexes to improve delivery.

III. The COVID-19 Pandemic

39. The spread of SARS-CoV-2 has resulted in an infectious disease outbreak on a scale not experienced in living memory, and it is not yet over. As we experienced with the Ebola Virus Disease outbreak of 2014, there are many lessons to be identified from biological events such as large scale infectious disease outbreaks. Lessons are still being learned and some may not yet be identified. Areas of technological progress that have direct relevance to the COVID-19 pandemic, or that have come about as a result of responding to the pandemic, and as such have relevance to Article VII include:

- The requirement to strengthen national capacities for response and preparedness; Ensuring the WHO has an appropriate and implementable mandate for responding to and investigating outbreaks;
- Strengthening infectious disease surveillance, monitoring and early warning systems;
- Improving information sharing;
- Investing in new research and development.

A. Disease Surveillance and Monitoring

40. The requirement for effective disease surveillance and monitoring has been of critical importance throughout the COVID-19 pandemic. The UK Health Security Agency (UKHSA) carry out detailed variant surveillance analyses, which contribute to the variant risk assessments and designation of new variants of concern (VOC) and variants under investigation (VUI). Many factors of viral evolution are monitored to determine new variants and subsequently assess their impact on diagnostic and therapeutic targets and biological risk assessment and management measures. Data covering a wide range of biological properties

are assessed including; changes in transmissibility, severity or immune evasion, growth rate and transmissibility, which could lead to a displacement of the current dominant variant. These reports which detail information covering genomic diversity, epidemiology, growth rates, secondary attack rates and hospitalisation are published by UKHSA on a regular basis[3,4].

41. Strengthening global surveillance of variants will be important in understanding the risk from new waves of disease emerging. Current genomic surveillance strategies are highly variable between countries and in many cases genomic data is not shared on public databases[5]. Strengthened and better aligned surveillance would be mutually beneficial in detecting and understanding emerging variants and their spread. BTWC States Parties should continue to proactively engage with and strengthen collaboration with the WHO, WOAH and FAO to share best practices relating to epidemiological surveillance.

B. Testing and Diagnostics

42. In response to the COVID-19 pandemic, the UK's COVID-19 testing capacity has vastly expanded through establishment of test facilities within the National Health Service (NHS), academia, universities, lighthouse facilities, the military and other private and non-profit community sectors[6]. This includes the largest network of diagnostic testing facilities in British history. Part of this capability was the establishment of several Lighthouse laboratories, which were high throughput facilities dedicated to COVID-19 testing for NHS Test and Trace.

43. Real-time PCR, from an extracted throat and nasal swab, is the gold standard used by the majority of diagnostic laboratories for COVID-19. The development of Endpoint PCR (ePCR) in a UK Lighthouse Laboratory, a technology adopted from industry, is one option being utilised to scale and speed up PCR testing. A single ePCR line has the potential to run over 15,000 samples concurrently, and a testing capacity of over 150,000 samples daily. ePCR is used alongside real-time PCR in UK Lighthouse laboratories to increase testing capacity with minimal facility and operational adaptations[7]. It has been suggested that the scalability and performance of ePCR may have the potential to allow for routine whole-population diagnostic monitoring during a pandemic using few centralised testing labs[7].

44. In addition to PCR based testing, the lateral flow test is a widespread, readily accessible and user-friendly testing option based on antibody technology. Lateral flow tests have played an important role in controlling the COVID-19 pandemic in many industrialized countries as well as resource-limited settings throughout the global response to COVID-19. Most rapid point of care (POC) diagnostic tests do not meet the quality standards required to replace centralized laboratory-based tests[8]. However, lateral flow tests are a popular POC diagnostic that has been widely used in combination with PCR based techniques to confirm SARS-CoV-2 infection[9]. The widespread public acceptance and overall success of lateral flow tests for mass POC diagnostics has accelerated research into similar technologies for a whole range of infectious and non-infectious ailments, such as cancer, organ function monitoring, sepsis and concussion.

[3] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1063424/Tech-Briefing-39-25March2022_FINAL.pdf

[4] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1057359/Technical-Briefing-37-25February2022.pdf

[5] Z. Chen et al. Global landscape of SARS-CoV-2 genomic surveillance and data sharing. Nature Genetics volume 54, pages499–507 (2022).

[6] https://www.gov.uk/government/news/two-new-megalabs-to-open-in-2021-to-transform-the-uks-diagnostic-facilities

[7] J. Roix *et al*. Evaluation of endpoint PCR (EPCR) as a central laboratory based diagnostic test technology for SARS-CoV-2. 2021.

[8] V. Sunkara, *et al*. Lab-on-a-Disc for Point-of-Care Infection Diagnostics. Acc.Chem. res., 54 (2021);

[9] Zhou, Y, *et al***.** Point-of-care COVID-19 diagnostics powered by lateral flow assay. 2021, TrAC Trends in Analytical Chemistry, Vol. 116452.

C. Genetic Sequencing

45. Whole genome sequencing (WGS) and the genotyping of variants can aid tracking disease transmission and lineages during an outbreak, especially when combined with geographical data[10]. Throughput, resolution, scalability, flexibility and affordability have continued to improve for high throughput sequencing technologies. As such, whole genome sequencing has played a pivotal role in the global response to the COVID-19 pandemic. Since the first genome sequence of a new coronavirus associated with human respiratory disease was published by Chinese scientists in early 2020, genetic sequencing of COVID-19 and subsequent variants has become commonplace in many countries[11]. The benefits of sequence monitoring were highlighted in the UK when the B.1.1.7 lineage was identified due to sequencing surveillance being conducted in London, where an increase of B.1.1.7 cases coincided with an increase in S gene target failures[12]. Other benefits include; using sequence data to shape emergency and longer term responses to infectious disease outbreaks, enabling preparation or predictive measures for future events, routine sequence monitoring prior to or during outbreaks could enable earlier identification of the causative agent, enabling tracking of transmission of known lineages and identification of emerging variants or variants with enhanced biological properties[10,12,13]. However, cost is still a significant limiting factor and generally, only a small proportion of confirmed positive samples are sequenced and assigned a lineage, this potentially means other circulating or new lineages may be missed[13].

46. A related well-established technology that can provide complementary high throughput data to whole genome sequencing but in a lower cost and more time efficient manner is genotyping. This uses a small panel of single nucleotide polymorphisms (SNP) to assign lineage to COVID-19 positive samples. Genotyping has been widely used in the UK and although will not produce full sequence information it can accurately assign a variant to a positive sample, which is sufficient to identify or rule out transmission routes to monitor viral spread. Using genotyping technology for real-time monitoring of COVID-19 variants can facilitate emergency responses and provide information for epidemiological studies and predicative modelling for future outbreaks. The main drawback of genotyping and a key reason why it would not be sufficient to replace the requirement for whole genome sequence surveillance is that it relies upon an up to date reference library of full genome sequences to screen against [10,13]. UK trials began with genotyping target panels in March 2021, and since then genotyping results have become a method of rapid identification of the Delta variant[14]. As of early August 2021 genotyping had been used to identify the variants Alpha, Beta, Delta and Gamma[15.]

D. Big Data, Machine Learning and Artificial Intelligence

47. Rapid decision-making technologies have been in demand to facilitate the national and global response to the spread of COVID-19[16]. This encouraged the development of more intelligent, highly responsive, and efficient detection methods. Algorithms have been

[10] E.L. Stevens *et al*. The Public Health Impact of a Publically Available, Environmental Database of Microbial Genomes. Frontiers in Microbiology, 2017, 8(808).

[11] Wu, F., Zhao, S., Yu, B. *et al*. A new coronavirus associated with human respiratory disease in China. Nature 579, 265–269 (2020). https://doi.org/10.1038/s41586-020-2008-3.

[12] E. Volz *et al*. Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England. Nature, 2021, 593(7858), 266-269.

[13] H. Harper *et al*. Detecting SARS-CoV-2 variants with SNP genotyping. PLOS ONE, 2021, 16(2), e0243185.

[14] Public Health England. SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 15. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993879/Variants_of_Concern_VOC_Technical_Briefing_15.pdf

[15] Public Health England. SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 21. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1012644/Technical_Briefing_21.pdf

[16] Vaishya, Raju, *et al*. "Artificial Intelligence (AI) applications for COVID-19 pandemic." Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14.4 (2020): 337-339.

developed for the automatic and accurate classification of COVID-19[17]. Diagnosis can involve the detection of pneumonia in COVID-19 patients but high diagnostic accuracy is difficult[18]. Artificial Intelligence (AI) and computer vision methods have been applied to extraction of features from radiological images, to provide diagnosis ahead of pathogenic tests, thus providing disease management within the critical time[17].

E. Vaccines and Therapeutics

48. The COVID-19 pandemic has driven scientists, regulators and policy makers to take an approach to vaccine development like no other. This will no doubt provide key lessons for accelerated vaccine development and production in response to future biological threats. Emerging viruses such as SARS-CoV-2, avian influenza and Ebola in recent years have driven the research community to focus on emerging zoonotic viruses and associated vaccine development[19]. The speed with which multiple SARS-CoV-2 vaccines were developed, tested and authorised for use in the UK was influenced by; this depth of existing research into Coronaviruses and new generation vaccines, increased funding and an adapted UK approval process[20]. Lessons identified in previous outbreaks which were declared a Public Health Emergency of International Concern have been learnt and new approaches have been developed, in particular, the new regulatory pathway enabling the rapid approval for emergency use of vaccines to treat COVID-19. The Human Medicine Regulations (MHR) 2012 is the UKs core legislation which regulates medical products, changes were made to this in 2020 to allow temporary authorisation of a unlicensed product (COVID-19 vaccine), subject to safety, quality and efficacy as defined by the MHRA[22]. In 2020 the UK's Medicines and Healthcare products Regulatory Agency, the MHRA, used a regulatory process known as a 'rolling review'. A 'rolling review' can be used to complete the assessment of a promising medicine or vaccine during a public health emergency in the shortest time possible. Data on the safety, quality and effectivity of the Pfizer mRNA vaccine, including lab and clinical trials, manufacturing and quality control was submitted to the MHRA between 1st October and 2nd December. The MHRA expert scientists and clinicians reviewed data from the laboratory pre-clinical studies, clinical trials, manufacturing and quality controls, product sampling and testing of the final vaccine and also considered the conditions for its safe supply and distribution. This process lead to the first COVID-19 vaccine for the UK, developed by Pfizer/BioNTech, being granted temporary authorisation from MHRA on 2nd December 2020 for use in the UK[21]. Temporary authorisation is not the same as standard marketing authorisation that is required for medicines to be marketed, under temporary authorisation the product is not considered to be fully licenced. Temporary authorisation lasts a fixed year, within which terms and obligations are defined, such as the requirement of further studies. Temporary authorisation can be converted to standard marketing authorisation following further data being submitted[22].

49. The first COVID-19 vaccine was a new generation mRNA vaccine, despite being the first mRNA vaccine approved, years of mRNA vaccine research existed which speed up development. Existing coronavirus research into SARS and MERS, included vaccine development and the identification of the spike protein as an effective vaccine antigen and how to stabilise it. The UK's Oxford-AstraZeneca viral vector vaccine similarly benefited from prior research, including the identification of the modified adenovirus viral vector[20].

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[17] Baghdadi, N. A., *et al*. An automated diagnosis and classification of COVID-19 from chest CT images using a transfer learning-based convolutional neural network. Computers in Biology and Medicine 144 (2022): 105383.

[18] Li D, Li S. An artificial intelligence deep learning platform achieves high diagnostic accuracy for Covid-19 pneumonia by reading chest X-ray images. I science. 2022 Apr 15;25(4):104031.

[19] D. Van Riel and E. De Wit. Next-generation vaccine platforms for COVID-19. Nature Materials, 2020, 19(8), 810-812.

[20] P. Ball. The lightning-fast quest for COVID vaccines — and what it means for other diseases. *Nature*, 2020, 589, 16-18.

[21] https://www.gov.uk/government/news/uk-medicines-regulator-gives-approval-for-first-uk-covid-19-vaccine

[22] Brodies LLP. The mechanics of medicines regulation - shining a spotlight on the MHRA vaccine approval decision. 2020.

50. Other vaccine types, such as inactivated or live attenuated vaccines, require the growth of large quantities of the virus, making development and manufacture more costly and time consuming. Additionally, in the case of COVID-19, this would need to be done in a high containment facility. In comparison, next generation vaccines (e.g. mRNA and viral vector) can begin development using the viral sequence, in the absence of the physical virus. New generation vaccines are not only quicker to develop but are also more easily adaptable, another benefit when facing new emerging viruses and new variants in the future19[19]. During the pandemic, increased funding allowed companies to run multiple stages of clinical trials and manufacturing in parallel to speed up the process[20].

IV. Enabling technologies

A. Nucleic Acid Synthesis

51. The efficiency and scalability of nucleic acid synthesis technology continues to advance. A development that has progressed throughout this ISP is the advent of more efficient bench top DNA synthesizers. These have become more commonplace in life science laboratories, expanding access to nucleic acid synthesis technology at lower cost and increased sequence length, without the need to use a sequence service provider. Policy makers now need to work with the scientific community to create governance measures that will not hinder the application of this enabling technology for beneficial and peaceful purposes supporting human, animal and plant health, but that will manage the risk of misapplication and deliberate misuse.

B. Peptide synthesisers

52. A scientific advancement that has seen much progress since the eighth Review Conference in 2016 is peptide synthesis technology. This technology is rapidly advancing, and the emerging fields of peptide-based drugs and biomaterials are increasing accessibility of custom peptide synthesis and driving down its cost. Peptide synthesis equipment is available at all scales, although currently from a limited number of manufacturers globally. However, companies providing custom peptide synthesis services are numerous and globally widespread. Peptide synthesis offers several advantages compared to exogenous peptide expression including: faster turnaround, removes the need for tag, reduces problems with low expression, removes risk of cloning errors, mistranslation or unwanted post-translational modification and it offers extensive modification options. There are however, some drawbacks associated with this technology and these include: limits to peptide length, lower yields for longer peptides, some peptide sequences are problematic, side reactions, secondary structure formation and problems with solubility. In addition to the advantages mentioned above, peptide synthesis can be applied to many research applications such as, research into peptide vaccines, peptide drugs, peptide based biomaterials, target validation, epitope mapping and structure and activity studies. Some recent developments of note include:

- Increased purity of commercially available amino acid building blocks increases yield and purity of peptides, which in turn allows for synthesis of longer peptides.
- The use of microwave or infrared heating and flow-based synthesis equipment has sped up the process to a matter of minutes[23,24], rather than hours, for each amino acid addition in a peptide chain. This can also increase the purity of the product.

[23] Hartrampf, N., *et al*., Synthesis of proteins by automated flowv chemistry. Science, 2020. 368(6494): p. 980-987.

[24] Simon, M.D., *et al*., Rapid Flov-Based Peptide Synthesis. ChemBioChem, 2014. 15(5): p. 713-720.

53. Chemistries to address problematic amino acid sequences have recently improved dramatically[25,26,27], making previously unobtainable sequences possible. Peptide ligation techniques are also advancing rapidly, which opens up the possibility of producing small proteins[28]. High throughput synthesis equipment can be used to make libraries of synthetic peptides with unlimited modification options for rapid screening to achieve desired characteristics.

54. The equipment ranges from small benchtop personal use scale, up through large benchtop research scale, high-throughput scale with multiple channels, floor standing pilot scale, and industrial scale, which can fill an entire room. The amount of crude protein produced in a single run from one of these pieces of equipment therefore ranges between milligrams and kilograms.

55. Companies providing gene synthesis services adhere to a harmonised protocol through the International Gene Synthesis Consortium (IGSC) to screen orders for sequences associated with dual use pathogens and toxins. It may be possible to establish a similar system within peptide synthesis companies to ensure that orders are screened for toxic products. However, peptides have an added level of complexity around their modifications and folding, which play an important role in their toxicity and action, which makes screening more difficult than for DNA sequences. Since the proliferation risk from custom ordered peptides might be considerably lower than that of synthetic DNA, the introduction of screening processes that would result in a significant burden for peptide synthesis companies may be considered disproportionate at this stage.

V. Convergence of technological areas

56. Advances in a number of technology areas, including synthetic biology, bioautomation, AI, machine learning, cloud- based laboratories, materials science, quantum and energetics are rapidly converging, which may consequently increase potential risks of misuse or misapplication of bioscience research. These convergences may also give rise to questions regarding the distinction between weapons of mass destruction and conventional weapons. A topic of discussion, which States Parties may wish to consider during the potential forthcoming ISP between now and the tenth Review Conference.

VI. Benefits and risk analysis

57. As with all biological related research, there are dual use considerations for all of the aforementioned fields of biotechnology and research, so the BTWC must keep pace with these rapidly advancing areas of S&T and have balanced discussions. We must ensure that benefits of biotechnology are considered along with any potential risks and that governance is proportionate and developed in partnership with the scientific and associated communities affected by biological risk assessment and management measures.

VII Future areas for technology watch

58. Precision medicine is a field of research that is growing considerably and has the potential to revolutionise how we treat human disease. Personalised treatments are developed taking into account genetic, environmental and lifestyle factors. In addition to the potential use of biotechnology such as gene editing in this way, BTWC States Parties should also

[25] Samson, D., *et al*., The aspartimide problem persists: Fluorenyimethyloxycarbonyl-solid- phase peptide synthesis (Fmoc-SPPS) chain termination due to formation of N-terminal piperazine-2, 5-diones. Journal of Peptide Science, 2019. 25(7): p. e3193.

[26] Jaradat, D.s.M.M., Thirteen decades of peptide synthesis: key developments in solid phase peptide synthesis and amide bond formation utilized in peptide ligation. Amino Acids, 2018. 50(1): p. 39-68.

[27] Paradís-Bas, M., J. *et al*., The road to the synthesis of "difficult peptides". Chemical Society Reviews, 2016. 45(3): p. 631-654.

[28] Agouridas, V., *et al*., Native Chemical Ligation and Extended Methods: Mechanisms, Catalysis, Scope, and Limitations. Chemical Reviews, 2019. 119(12): p. 7328-7443.

remain mindful of the use of biometric and sequence data and consider the security implications of storing and using such data. This is an innovative field of research still in its infancy, however it does present with opportunities for technological convergence and could provide immeasurable benefits to human health on a global scale. As with many of the tools and technologies presented herein, these benefits should not be limited by risk management and governance measures. In fact, benefits should be protected and encouraged, while early consideration of risk assessment and management measures should provide assurance that everything possible has been done to minimise the risk of misapplication or deliberate misuse of precision medicine.

United States of America

I. Introduction

59. Since the previous review of scientific and technological developments in 2011[29], no new discoveries or technologies have fundamentally altered the nature of life sciences research or raised questions concerning the scope of the Convention. However, the pace of developments identified in 2011 has continued to accelerate, expanding the possibilities not only for benefits to public health and medicine, agriculture, the environment, and other peaceful applications, but also for misuse for purposes banned by the Convention. Individual scientific discoveries and technological tools continue to grow more accessible, to develop more rapidly, and to converge with other disciplines such that the threat from biological weapons and our ability to respond effectively is evolving rapidly. This paper highlights several major advances and trends in the life sciences over the last decade and examines their implications for the Convention.

II. Specific S&T developments since 2011

A. Advances in genome and gene editing technology

60. Altering the genetic material of natural organisms is not new. Humans have been doing this for thousands of years through selective breeding of crops and livestock. However, 20th century insights into heredity, followed by the ability to directly manipulate genetic material have enabled the development of "biotechnology" – technology that applies to and/or is enabled by life sciences innovation or product development, for example, the intentional harnessing of genes and other cellular or biomolecular processes to create technologies, medicines, and products.

61. Since 2011, scientific and technology developments continued to advance the accuracy, speed, and understanding of genome editing for a wide range of beneficial applications. CRISPR/Cas technology is a notable development that led to a Nobel Prize in 2020 and is used around the world[30]. This genome editing tool and others like it enable research in the life sciences to be carried out with a level of precision, efficiency, and scope that was not previously possible. Further, the advances in precise genome editing technologies are creating new or improving existing clinical therapies. For example, clinical data is demonstrating how genome or gene editing tools may be able to cure patients with diseases with known genetic disorders (like sickle cell disease) or to target specific parts of a patient's body (like cancer cells)[31]. Beyond the health and medical fields, genome editing technologies can be and have been used to precisely introduce desirable traits for sustainable and resilient food production – like new oilseed varieties that have higher levels of omega-3

[29] BWC/CONF.VII/INF.3 - New scientific and technological developments relevant to the Convention – Background information document submitted by the Implementation Support Unit.

[30] Ledford and Callaway. "Pioneers of revolutionary CRISPR gene editing win chemistry Nobel." *Nature News*, 7 October 2020. https://www.nature.com/articles/d41586-020-02765-9.

[31] https://www.cancer.gov/about-cancer/treatment/research/car-t-cells and https://www.synthego.com/blog/car-t-crispr-cancer#what-you-need-to-know-about-crispr-and-car-t-cells.

fatty acids or grain crops that are more tolerant to drought. Similarly, genome editing technology makes it more feasible to convert micro-organisms into cellular factories for desired products (i.e., metabolic pathway engineering).

B. Advances in vaccine technology

62. Vaccines protect against the spread of disease by providing immunity to individuals. Since the vaccines for smallpox, cholera, anthrax, and plague were developed over a century ago[32], vaccine technology has continued to improve and be a cornerstone for disease prevention and control. Historically, vaccines have taken approximately 10-20 years to develop, but in 2020 multiple safe, effective, and high-quality vaccines against a novel virus (SARS-CoV-2) were researched, developed, and manufactured at scale in just one year from when the outbreak was reported, by leveraging decade-long basic research in a number of fields. A combination of complementary strides in the scientific knowledgebase, DNA synthesis technology, vaccine research using structural biology tools, advanced manufacturing, bioinformatics, longstanding investments in biological defense research and development, and international collaboration all enabled this truly remarkable achievement.

63. One specific scientific development that went beyond accelerating the traditional vaccine technologies, such as inactivated or attenuated viruses, was the advent of mRNA- and viral vector-based vaccines. These vaccine platforms bypass the need to pre-produce and package materials like proteins by directly delivering molecular *instructions* into patients whose own cells in turn produce the needed antigens to build immunity. This process also enables the use of manufacturing technologies that also appear promising for rapidly addressing other emerging biological threats. Prior to COVID-19, no vaccines had been authorized using mRNA vaccine technology and only a handful of viral vector vaccines (for Ebola in humans and for several veterinary diseases) were approved. One key safety and security benefit of this vaccine technology is that the manufacturing process removes the risks associated with handling, and growing large amounts of, live or attenuated virus, as vaccine development can be performed without those materials. These technologies are now being explored for a variety of other diseases, such as HIV, influenza, and Nipah virus and it is theoretically possible that the technology could be applied to vaccines for childhood immunizations, other microbial pathogen threats, and to treat noncommunicable diseases including cancer. Furthermore, such "platform technologies" may be readily adaptable for use if a novel pathogen emerges as a public health threat.

C. Advances in genomic sequencing

64. Genome sequencing and especially whole genome sequencing – the ability to read the entire genetic instructions of an organism or virus – is increasingly important for a broad spectrum of applications. For instance, sequencing is used during the public health response to a disease outbreak to detect and track mutations, for development of medical treatment tailored for a specific person suffering from cancer or other conditions with a genetic basis ("precision medicine"), and for environmental conservation efforts by identifying and monitoring invasive species.

Disease outbreak response

65. Genomic sequence data from samples taken from patients or the environment can be used to detect outbreaks and novel zoonotic or other pathogens that pose a risk to health security, support efforts to develop vaccines and diagnostics, support decision making for non-pharmaceutical interventions, and carry out ongoing surveillance to identify new variants. The use of genomic sequencing to advance public health has grown rapidly, particularly during the COVID-19 pandemic.

66. Since genome sequencing works by reading the genetic material in a sample, sequencing can be widely used to identify novel pathogens that were not detected by agent-based diagnostic methods. For example, genome sequencing was used to identify SARS-CoV-2 – a new virus – as the causative agent of a cluster of unknown pneumonia cases in

[32] https://www.immune.org.nz/vaccines/vaccine-development/brief-history-vaccination.

Wuhan, China in early 2020. Knowing the genome sequence of the virus spurred the rapid development of diagnostics, therapeutics, and vaccines that are now being used in countries worldwide.

67. Ongoing genomic sequencing of patient samples linked to data regarding surges in cases or clinical outcomes during a disease outbreak can track the emergence of new variants, aid in risk assessments, and monitor how they spread. During the COVID-19 pandemic, sequencing paired with other data enabled the identification of new variants of concern globally, allowing countries to identify, assess, and track the spread of variants with different properties, such as the initial Alpha variant and successive variants such as Omicron. This approach has allowed countries to implement changes in public health measures and modify existing diagnostic tests and medical countermeasures, as needed.

Precision medicine

68. The wide availability of genome sequencing allows doctors and researchers to more accurately predict which treatment and prevention strategies for a particular disease will work for specific groups or individuals based on their genetic variabilities. This approach contrasts with the traditional "one-size-fits-all" approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals.

69. Cancer is the target disease of some of the most promising precision medicine approaches available today. Cancer usually comes about through the gradual accumulation of genetic changes (mutations) in genes that control cell growth. Depending on where in the body the cancer arises and the types of genetic changes the cells accumulate, different types of cancer can have very different genetic profiles and respond differently to treatments. By comparing the DNA from a patient's tumor to that of their normal cells, researchers can learn how the cancer came about and what treatments might be most effective[33]. By tracking the genetic profiles of their patients' tumors, doctors can learn which treatments work best for which patients.

D. Advances in information processing

70. The life sciences have greatly benefited from new computing technology that enables rapid processing of large quantities of data with techniques ("machine learning") that allow progressively more accurate conclusions to be drawn. Related advances in computational modeling have been used for predicting the spread of disease outbreaks and the impact of restrictions on disease spread, as well as associated impacts on transportation, local economies, and other factors. Further computational modeling provides a means of rapidly identifying promising pharmaceutical candidates.[34] Two recent examples relevant to the Biological and Toxin Weapons Convention are predictions of protein structure and attribution of genetic engineering.

Protein folding

71. Proteins are chains of amino acids that are present in all living organisms and include many essential biological compounds such as enzymes, hormones, and antibodies. Proteins form a three-dimensional shape that is necessary to their function. Predicting the shape of a protein is critical to understanding exactly how it carries out its task and how this action may be modified, blocked, or enhanced in order to treat disease.

72. Unfortunately, the number of different shapes that a given protein could take based on its amino acid sequence is astronomical. Until recently, scientists have depended on expensive and time-consuming laboratory methods to determine the structure of a protein

[33] Tsimberidou *et al*. "Review of Precision cancer medicine: Evolution of the treatment paradigm." *Cancer Treat Rev*. 31 March 2020. https://pubmed.ncbi.nlm.nih.gov/32251926/.

[34] U.S. Department of Energy National Virtual Biotechnology Laboratory Technical Report, June 2022. https://science.osti.gov/-/media/nvbl/pdf/NVBL_Technical_Report.pdf".

experimentally. Such efforts have identified the structures of about 170,000 proteins over the last sixty years, out of the approximately 200 million proteins estimated to exist in nature[35].

73. In August 2022, the artificial intelligence company DeepMind unveiled the likely structures of 200 million known proteins, from organisms ranging from bacteria to humans. This remarkable result comes from the artificial intelligence program AlphaFold, which has substantially advanced the protein-folding field by more accurately predicting the three-dimensional shapes of proteins from their amino acid sequences than previous technologies[36]. Many applications will still require additional experimental evidence to validate these structures, including to aid in rapid pandemic response and other drug discovery efforts. However, this development provides a significant head start for discoveries. The predicted protein structures were released into an existing free database through a partnership with the European Molecular Biology Laboratory's European Bioinformatics Institute.

Genetic engineering attribution

74. The rapid development of techniques for synthesizing genetic material or editing naturally occurring sequences has raised concerns that such genetic engineering techniques might be misused to produce a biological weapon, for example, by making a naturally occurring pathogen strain more infectious or more survivable in the environment. Addressing these concerns poses two separate challenges – detecting that a genetic sequence has been engineered and determining who was responsible ("attribution").

75. The FELIX project in the United States is developing new experimental and computational tools to identify indicators of genetic engineering.[37] Under the UN Secretary-General's mechanism for investigating alleged biological attacks, efforts are underway to develop an international laboratory network that would be capable of detecting modified genetic sequences in pathogens using specialized information processing tools.

76. Considerable progress has been made in developing tools for attribution of genetic engineering. In 2020, more than 300 teams from around the world took part in a data science competition to identify the laboratory of origin of engineered genetic sequences with the highest possible accuracy.[38] Pulling from open-source published sequences, top accuracy scores exceeded the previous state of the art. Winning teams adopted a variety of different technical approaches, demonstrating the diversity of information processing methods that can be applied to genetic engineering attribution, as well as the potential for new machine learning approaches to further improve on existing tools. All computer software from the winning submissions will be made publicly available.

E. Advances in the synthesis of biological molecules

77. Prior to the 1970s, biological materials needed to be obtained from living animals, plants, or other organisms. The recombinant DNA revolution made it possible to directly synthesize such materials without needing to collect, grow, or raise the original organism. One example is antibody production for pharmaceutical purposes, such as antibody treatments for rheumatoid arthritis (like Adalimumab). While antibodies can be harvested from infected animals, many can now also be manufactured directly by human or other cell lines in the laboratory which can lower the products' cost, increase manufacturing speed, and minimize patient allergic reactions.

78. Over the past decade, the synthesis of biological molecules has become less expensive and more widespread, and the type of products and the ways to produce them has continued to expand. Biological molecules like DNA and other nucleic acids and proteins can be

[35] Robert F. Service. "The game has changed. AI triumphs at solving protein structures." *Science*, 30 November 2020. https://www.science.org/content/article/game-has-changed-ai-triumphs-solving-protein-structures.

[36] Jumper, J., Evans, R., Pritzel, A. *et al.* "Highly accurate protein structure prediction with AlphaFold." *Nature*, vol. **596**, 2021, pp. 583–589. https://doi.org/10.1038/s41586-021-03819-2.

[37] https://www.iarpa.gov/research-programs/felix.

[38] https://altlabs.tech/geac/.

chemically synthesized in longer lengths and lower costs around the world than ever before. Many companies now offer custom nucleic acid synthesis.

79. Advances in nucleic acid synthesis technologies have facilitated easy-to-use, efficient, and accurate systems to study viruses and how they cause disease, to understand what new mutations may mean for virulence or the ability to evade immune responses, and to standardize the genomic blueprint from which to grow virus stocks for experimentation, therapeutic, and vaccine development. At the beginning of the COVID-19 pandemic, nucleic acid synthesis technology enabled the SARS-CoV-2 virus to be synthesized within a month after the genome sequence was published on January 11, 2020.

80. Other biological molecules like lipids, large proteins, or biochemicals can be synthesized directly or in specifically engineered organisms to manufacture certain products. These products can range from medical, agricultural, and other commercial applications, such as the manufacturing plant-based heme (soy leghemoglobin) in yeast to flavor plant-based foods[39] or bioplastics (polyhydroxyalkanoates) that are potentially more eco-friendly alternatives to traditional plastics.

III. Trends in Science and Technology

81. In addition to specific scientific and technical advances, such as those highlighted in the previous sections of this paper, there are more general trends in science and technology that individually and collectively are relevant to the Convention. Among these are: systems biology, which combines information from several specialized approaches; greatly enhanced international collaboration; rapid accretion and assimilation of data; creation of platforms for open sharing of data; and rapid open publication of results.

82. By combining information gathered from different highly specific approaches ("omics" methods), researchers are able to obtain a much better understanding of how biological systems function, interact, and are in fact interdependent. This can provide insights into basic biology, mechanisms of disease, and potential drug targets. For example, researchers are applying these approaches to help identify treatment candidates that work across multiple coronaviruses[40] or to help identify the genetic basis for heart disease[41]. The desire to better understand the complexity of biological systems, accelerated by the urgency of responding to the COVID-19 pandemic, is fostering greater interdisciplinary research and collaboration within and among countries. Key examples are the CEIRR Network[42] (Centers of Excellence for Influenza Research and Response Network), a research network created to study influenza and combat influenza outbreaks, and the CREID Network[43] (Centers for Research in Emerging Infectious Diseases), a coordinated group of research centers situated around the globe where emerging and re-emerging infectious disease outbreaks are likely to occur.

83. The rapid pace of research and creation of large sets of data is leading to repositories that enable this information to be more accessible. During the COVID-19 pandemic, platforms like GISAID[44] allowed public accessible, real-time sharing of sequences and NextStrain[45], GenBank[46] and other international nucleotide sequence database collaborations facilitated open, real-time sharing of genomic information for SARS-CoV-2 sequences, allowing researchers and public health officials to better track the course of the pandemic and identify variants. In addition, the Protein Data Bank (www.wwpdb.org) was populated with hundreds of SARS-CoV-2 protein structures from x-ray centers, which allowed targets to be

[39] https://faq.impossiblefoods.com/hc/en-us/articles/360034767354.

[40] Gordon *et al*. "Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms." *Science*, vol. 370, is. 6521, 2020. pp. eabe9403. doi: 10.1126/science.abe9403.

[41] Gonzalez-Teran et al. "Transcription factor protein interactomes reveal genetic determinants in heart disease." Cell, vol. 185, is. 5, 2022, pp. 794-814.e30. https://doi.org/10.1016/j.cell.2022.01.021.

[42] https://www.ceirr-network.org/

[43] https://creid-network.org/

[44] https://gisaid.org/

[45] https://nextstrain.org/

[46] GenBank Overview (nih.gov)

identified for therapeutics design. Data repositories also help computational biologists develop tools for processing large amounts of data in order to extract new insights, such as changes in the composition or characteristics of circulating SARS-CoV-2 viruses, and impact of any anticipated changes in public health response strategy at local, national, or global level.

84. Traditionally, research results were published in technical journals after careful review by panels of experts ("peer review") and access to the journal articles required a subscription. The need for a rapid response to the COVID-19 pandemic, however, greatly increased the need and pressure for greater and immediate public accessibility to research results. In response, many journals opened access for COVID-19-related publications. Sites for sharing draft research articles were developed, which although not peer-reviewed, enabled more widespread use of data in-time sensitive pandemic response and public health decision making. Although this development allowed knowledge to be shared more rapidly and widely, the lack of quality control meant that researchers and public health officials needed to be especially alert for poor or inaccurate work.

85. Although the COVID-19 pandemic fostered greater international collaboration, sharing of data, and access to research results, it also stimulated interest in strengthening national capabilities for research and development related to emerging and high-consequence pathogens. For example, numerous countries announced plans to build new high and maximum containment laboratories. Such laboratories require extensive safety and security measures. Not only are they expensive to build, but they also require dedicated and sustained funding and expert staffing to ensure that they are safely and properly operated, maintained, and secured.

IV. Implications for the Convention

86. Individually, each of the advances described in this paper makes a substantial and growing contribution to our efforts to understand how living organisms work. Applying this knowledge for peaceful purposes is yielding substantial and growing benefits for humankind, including improving public, animal, and environmental health, as well as producing better and less expensive food. Collectively, the impact can only be described as revolutionary.

87. It cannot be overemphasized that improving the ability to prevent, detect, and respond to natural outbreaks of infectious disease also helps to build defenses against both accidents and the deliberate use of disease as a weapon. A strong public health system prepared to prevent, detect, and respond to infectious disease threats can help to deter the use of biological weapons by reducing their potential effectiveness and impacts, including in the event that a biological weapon is used, to minimize the deaths, injuries, and economic damage that may result.

88. On the other hand, it has long been recognized that advances in understanding living systems can be used not only for beneficial purposes, but also to develop ways to disrupt those systems; such knowledge is "dual use." For this reason, the Convention prohibits those actions that have no justification for peaceful purposes.

89. The advances described in this paper are each "dual use" in character. Any of them could be misused for biological weapons purposes. The comprehensive scope of the Convention covers these advances, but continuous review is necessary. In particular, in planning and conducting life sciences research, careful oversight is needed to preserve the benefits of such research while minimizing the risk of misuse of the knowledge, information, products or technologies provided by such research.

90. In summary, the actual and potential benefits of the advances in science and technology described in this paper are numerous, but risks do exist that need to be carefully monitored, including through creation of a BWC science and technology advisory mechanism, so that, if necessary, appropriate safeguards are in place.